REMARKS

Claims 1 and 4-9 are pending in the instant application. Claims 1 and 4-9 have been rejected. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Withdrawn Rejections

Applicants acknowledge that the rejection based on written description under 35 U.S.C. §112, first paragraph, has been withdrawn.

II. Rejection of Claims Under 35 U.S.C. §103

Claims 1, 4-5 and 9 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Xu et al. ((1998) *Nucleic Acids Res.* 26:2034-2035), Mattioni et al. ((1994) *Meth. Cell Biol.* 43:335-352) and Hull et al. ((1995) *Meth. Mol. Biol.* 49:125-141).

The Examiner maintains that with these references in hand it would have been obvious to one of ordinary skill in the art to combine the teachings and arrive at a fusion protein as recited by claims 1, 4-5 and 9. It is suggested that, based on the method of Xu et al., it would have been obvious to those skilled in the art to replace the reporter and the repressor taught by Xu et al. (*i.e.*, enhanced green fluorescent protein, EGFP, and enhanced blue fluorescent protein, EBFP) with the β-glucuronidase taught by Hull et al. and the enzyme repressors taught by Mattioni et al. to construct a fusion protein comprising β-glucuronidase and a hormone binding domain, such as the GR-HBD, linked through a predetermined protease cleavage site such as that of a specific caspase and use it to determine the presence of said protease. It is further suggested that one would have been motivated to do so in order

to develop an alternate system to that developed by Xu et al., *i.e.*, an enzyme-based fusion protein and assay, as opposed to the fluorescent protein-based fusion protein and assay as developed by Xu et al. In response to Applicants' arguments filed 10-6-04, the Examiner suggests that the only difference between the fusion protein of Xu et al. and the instant fusion protein is that the proteins used have different properties and therefore the means of detecting the liberated protein is different. Accordingly, it is suggested that the overall principle in the instant invention is identical with that of Xu et al. *i.e.*, the properties of the two individual proteins are changed or inactivated as long as they are linked together and demonstrate their specific characteristic only after being separated due to the cleavage. Applicants respectfully traverse this rejection.

Applicants maintain that the cited references fail to meet the basic tenets set forth by MPEP §2141 when applying 35 U.S.C. 103. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the *desirability* of the combination. In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). See MPEP 2143.01. The cited references fail to suggest such desirability. Specifically, while Hull et al. teach that β-glucuronidase can tolerate large N- and C-terminal fusions and has a wide variety of substrates useful for detecting activity (see page 126), this reference fails to teach or suggest that β-glucuronidase is a substitute for fluorescent reporter proteins. Further, Xu et al. indicate that the assay taught therein is a convenient assay with the major advantage being the use of fluorescent proteins which require no cell staining. The assay is touted as being useful for continuously monitoring live cells during the course of an

experiment (see page 2035, column 1, ¶2). Further, this reference suggests alternative colored GFP, such as yellow fluorescent protein, for use in combination with the EGFP and EBFP to provide more flexibility in generating a variety of constructs (see page 2035, column 2, ¶1). However, nowhere does this reference teach or suggest that β-glucuronidase is a substitute for fluorescent reporter proteins. Thus, Applicants find no reasonable basis for the Examiner's conclusion that one of skill would be motivated by these teachings to develop an alternate system to Xu et al. which employs the use of β-glucuronidase of Hull et al. as there is no suggestion of the *desirability* to do so.

Further, MPEP 2144.06 indicates that in order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on Applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. In re Ruff, 256 F.2d 590, 118 USPQ 340 (CCPA 1958). Hull et al. teach that β-glucuronidase has a wide variety of substrates which can be used to stain a cell; however, monitoring real-time changes in activity in living cells over time is not described. Xu et al. teach that the advantages of using a fluorescent protein include monitoring living cells over a period of time and no cell staining. Therefore, while GFP proteins and β-glucuronidase both function as reporter proteins, the prior art does not consider these reporter proteins equivalent substitutes which can readily replace one another in all applications. To maintain the advantages of the system of Xu et al., the skilled artisan would have little motivation to select β-glucuronidase over a fluorescent reporter, as β-glucuronidase is not an equivalent substitute for a GFP in the system of Xu et al. Therefore,

given that the cited art fails to teach, suggest, or motivate the skilled artisan to combine the teachings therein, it is respectfully requested that this rejection be reconsidered and withdrawn.

Claims 6-8 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Xu et al., Mattioni et al. and Hull et al. as applied to claims 1-2, 4-5 and 9 and further in view of the common knowledge in the art.

The Examiner suggests that using the teachings of Xu et al., Mattioni et al. and Hull et al. it would have been obvious to those skilled in the art to have multiple reporter domains such that the signal intensity obtained from the reporter domain, whether via fluorescence as in Xu et al. or activity of the reporter enzyme as in the instant case, would be more intense and its detection be easier. The Examiner further suggests that because of the simplicity and ease of use of the technique it would have been obvious to one of skill in the art to use multiple protease cleavage sites and detect the presence of multiple sets of proteases. The Examiner indicates that one of skill in the art would have been motivated to do so in order to develop intense signal during the assay. Applicants respectfully traverse this rejection.

Applicants maintain that claims 6-8 fail to be obvious in light of the teachings of Xu et al., Mattioni et al. and Hull et al. for the reasons set forth above in that these references fail to teach, suggest, or motivate the skilled artisan to combine the teachings of the cited references to arrive at the instant inventive chimeric protein of claim 1. Thus, when an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). See MPEP

§2143.03. Thus, withdrawal of the rejection of claims 6-8 is respectfully requested.

III. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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